STATE OF MICHIGAN
IN THE SUPREME COURT

TAMARA TAYLOR and LEE ANN RINTZ,

Plaintiffs-Appellees,

v.

A.H. ROBINS COMPANY, INCORPORATED, WYETH AYERST LABORATORIES COMPANY and AMERICAN HOME PRODUCTS CORPORATION,

Defendants-Appellants,

and

GATE PHARMACEUTICALS, SMITHKLINE BEECHAM CORPORATION, et al.,

Defendants.

and

JUDITH H. ROBARDS and KENNETH W. ROBARDS,

Plaintiffs-Appellees,

v.

A.H. ROBINS COMPANY, INCORPORATED, WYETH AYERST LABORATORIES COMPANY and AMERICAN HOME PRODUCTS CORPORATION,

Defendants-Appellants,

v.

GATE PHARMACEUTICALS, SMITHKLINE BEECHAM CORPORATION, et al.

Defendants.

SCt 120624

Court of Appeals No. 217269
Wayne County Circuit Court
Case No. 97-731636-NP
Hon. Marianne O. Battani

Court of Appeals No. 227700
Washtenaw County Circuit Court
Case No. 99-5373-MN
Hon. David S. Swartz

Brief of Amicus Curiae Pharmaceutical Research Manufacturers of America In Support of Defendants

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BRIEF OF *AMICUS CURIAE*
PHARMACEUTICAL RESEARCH AND MANUFACTURERS OF AMERICA
IN SUPPORT OF DEFENDANTS

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QUESTION PRESENTED

Was it an appropriate exercise of legislative power for the Michigan legislature to decide in 1995 that a pharmaceutical manufacturer that complies with the new drug approval criteria of the Federal Food, Drug, and Cosmetic Act (FDCA), 21 U.S.C. § 301 et seq., has satisfied its duty of care to the drug consumer for the purposes of Michigan tort law?

Defendants answer: yes.

The Court of Appeals answered: no.

Amicus curiae answers: yes.

STATEMENT OF THE FACTS

In 1995, Michigan enacted MCL 600.2946(5), MSA 27A.2946(5), which provides that: "In a product liability action against a manufacturer or seller, a product that is a drug is not defective or unreasonably dangerous, and the manufacturer or seller is not liable, if the drug was approved for safety and efficacy by the United States food and drug administration." Section 2946(5) provides a defense to pharmaceutical manufacturers in product liability suits brought under Michigan law, if the drug product in question was approved by the United States Food and Drug Administration (FDA).[1] Put another way, section 2946(5) is a legislative pronouncement that, in Michigan, the duty of care owed by

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[1] The defense is not available if the manufacturer intentionally withheld from or misrepresented to FDA information concerning the drug, or if the manufacturer made an illegal payment to an FDA official or employee to secure or maintain approval of the drug. Plaintiffs have conceded at all stages of this litigation that neither exception applies in this case.

a pharmaceutical company to consumers of its products has been met if the pharmaceutical company has satisfied FDA that the drug is safe and effective.

The Michigan statute builds on earlier state and federal precedents that afforded at least a rebuttable presumption of safety to FDA-approved drugs. For example, in response to liability concerns, Congress in 1986 enacted an FDA compliance defense for childhood vaccines. See 42 U.S.C. § 300aa-22(b) (establishing burden of proof for recovery of compensatory damages); § 300aa-23(d) (prohibiting punitive damages). Most states, including Michigan before 1995, consider FDA approval directly relevant to the question of whether the duty of care has been met.[2] Commentators have urged for years that regulatory compliance be deemed an absolute defense in tort law.[3] In 1991, the American Law Institute concluded that—subject to three conditions—compliance with

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[2] See, e.g., Col. Rev. Stat. 13-21-403 (creating rebuttable presumption that a product was not defective if, at the time of sale, it complied with an applicable code, standard, or regulation); N.J. Stat. Ann. 2A:58C-4 (creating a rebuttable presumption that a warning approved by FDA is adequate); Ark. Code Ann. 16-116-105 (permitting introduction of evidence of compliance with any federal or state statute or administrative regulation existing at the time a product was manufactured and prescribing standards of design, inspection, testing, manufacture, labeling, warning, or instructions for use); Ohio Rev. Code Ann. 2307.80(C) (barring punitive damages against manufacturer of drug manufactured and labeled in compliance with FDA requirements); Or. Rev. Stat. 30.927 (barring punitive damages in a pharmaceutical case in which drug and labeling was approved by FDA, provided material information was not withheld or misrepresented); see generally Paul Dueffert, Note, "The Role of Regulatory Compliance in Tort Actions," 26 Harv. J. Legis. 175, 178 (1989) (discussing state statutes that provide a rebuttable presumption that a product is not defective if it complied with relevant safety standards).

[3] See, e.g., W. Kip Viscusi et al., "Deterring Inefficient Pharmaceutical Litigation: An Economic Rationale for the FDA Regulatory Compliance Defense," 24 Seton Hall L. Rev. 1437, 1478-80 (1994); Richard A. Epstein, "Legal Liability for Medical Innovation," 8 Cardozo L. Rev. 1139, 1151-54, 1157-58 (1987).

regulatory requirements imposed by an administrative agency should preclude tort liability.[4] Section 2946(5) tracks the ALI recommendation.

In October 1997, plaintiffs Tamara Taylor and Lee Anne Rintz filed suit in Wayne County Circuit Court "on behalf of themselves and all others similarly situated," alleging medical malpractice and product liability arising out of their use of the prescription drugs fenfluramine, phentermine, and dexfenfluramine. Fenfluramine hydrochloride is the generic name for Pondimin. Dexfenfluramine hydrochloride is the generic name for Redux. Although approved by FDA, these drugs were voluntarily withdrawn from the market in 1997. Phentermine hydrochloride, manufactured and sold under a number of brand names, including Fastin, was approved by FDA in 1973 and remains on the market. The defendants included the pharmaceutical companies that manufactured and sold these drugs. Plaintiffs Judith and Kenneth Robards brought an action involving the same drugs in the Washtenaw County Circuit Court.

In both cases, the pharmaceutical defendants moved for summary disposition on the basis of section 2946(5). Plaintiffs in both cases responded that section

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[4] The three conditions were: (1) the risk must have been placed under regulatory control by a specialized administrative agency with authority to monitor and assess risk and a mandate to impose related controls on enterprise behavior; (2) immunity should be available only if the enterprise complied with all regulatory requirements; and (3) immunity should not be available if the enterprise failed to disclose material information within its possession regarding risks. American Law Institute, Reporter's Study, II Enterprise Liability for Personal Injury (ALI Study) 95-97 (1991). The American Law Institute is a national membership organization of judges, lawyers, and law professors, selected from throughout the country on the basis of professional achievement and demonstrated interest in the improvement of law. For three quarters of a century, it has aimed "to promote the clarification and simplification of the law and its better adaptation to social needs, to secure better administration of justice, and to encourage and carry on (continued . . .)

2946(5) is unconstitutional—that it is an improper delegation of legislative power, and that it violates constitutional guarantees of open courts, due process and equal protection. The Wayne County court found section 2946(5) to be an unconstitutional delegation of legislative authority. The Washtenaw County court found section 2946(5) constitutional and granted summary disposition for the defendants. On November 30, 2001, the Court of Appeals consolidated the cases and ruled that section 2946(5) was an unconstitutional delegation of legislative authority. It accordingly affirmed the Wayne County decision and reversed the Washtenaw County decision. On December 21, 2001, Defendants-Appellants American Home Products Corporation, A.H. Robins Company, Incorporated, and Wyeth-Ayerst Laboratories Company (Defendants) filed an application for leave to appeal to this Court. On January 18, 2002, Plaintiffs-Appellees Tamara Taylor, Lee Anne Rintz, Judith Robards, and Kenneth Robards filed a combined reply opposing the application. On July 2, 2002, this Court granted leave to appeal.

INTEREST OF THE *AMICUS CURIAE*

The Pharmaceutical Research and Manufacturers of America (PhRMA) is a voluntary nonprofit association of the country's leading research-based pharmaceutical and biotechnology companies.[5] PhRMA members discover, develop, manufacture, and market almost all new prescription drug products in this country. In 2001, PhRMA members

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scholarly and scientific legal work." "About the American Law Institute," <www.ali.org/ali/thisali.htm> (visited March 1, 2002).

[5] Defendants SmithKlineBeecham Corporation and Wyeth are members of PhRMA.

expected to spend $30.5 billion to discover and develop medicines that will allow patients to lead longer, healthier, and more productive lives.[6]

Expanding theories of tort liability have adversely affected and will continue to adversely affect the development and availability of life-saving drugs. One of PhRMA's objectives is to ensure that state courts and legislatures considering issues of product liability for pharmaceutical products give appropriate weight to FDA's determinations regarding the safety and effectiveness of those products. This case is of particular interest to PhRMA because the Michigan statute at issue affords deference in the tort context to FDA's judgment that a new drug is safe.

ARGUMENT

The Court of Appeals found section 2946(5) unconstitutional, on the ground that it makes FDA the final arbiter with respect to whether a particular drug may form the basis of a product liability action in Michigan. Defendants argue that the statute is constitutional because it constitutes a legislative decision to adopt a factual determination, with independent significance, made by a non-legislative body with substantial relevant expertise. Defendants explain that (1) the Michigan Supreme Court has previously approved the practice of adopting schemes whereby factual determinations by non-legislative bodies trigger statutory consequences in Michigan, (2) courts across the country routinely uphold statutes that incorporate determinations of non-legislative bodies under the doctrine of "Independent Significance," and (3) incorporation of facts with independent

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[6] PhRMA, Pharmaceutical Industry Profile 2001, available at www.phrma.org (Industry Profile) at v (visited March 8, 2002).

significance is a common and constitutional legislative practice in Michigan. We agree with these arguments and do not revisit them here.

In opposing Defendants' application for leave to appeal, Plaintiffs devoted nearly ten pages to "the FDA process," stating – among other things – that FDA is "not up to the job of determining safety of drugs," that there is "no or inadequate monitoring of manufacturer studies," and that there are "significant pressures, from the manufacturers on the one hand, and sufferers of medical conditions on the other, to quickly rubber stamp and shortcut the approval process." In this brief supporting the defendants' appeal, PhRMA responds (as it did in its brief supporting Defendants' application for leave to appeal) by explaining the drug research and development process, the role of FDA in that process, and the nature and significance of an FDA determination that a particular drug product is "safe" and "effective." As explained below, the Michigan legislature's decision was both appropriate and rational.

The federal regulatory scheme governing development, testing, approval, and marketing of new drug products is nearly a century old. Modern food and drug law began with the Pure Food and Drugs Act of 1906.[7] In 1938, the Federal Food, Drug, and Cosmetic Act (FDCA), 21 U.S.C. § 301 et seq., which remains in place today, prohibited the marketing of any new drug not shown to be "safe for use under the conditions prescribed, recommended, or suggested" in its labeling.[8] In 1962, Congress amended the FDCA to require that new drugs also be proven effective, and gave FDA the authority to

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7 Pub. L. No. 59-384, 34 Stat. 768 (1906).

8 Pub. L. No. 75-717, § 505(d)(1), codified at 21 U.S.C. § 355(d)(1).

prescribe the tests that a manufacturer must perform before its product may be approved for marketing.[9] Over the last half century, numerous amendments have expanded, strengthened, and refined the regulatory scheme.[10] FDA now regulates virtually every stage in the life of a new drug, from preclinical testing in animals and human clinical trials before the drug can be marketed, to manufacturing, labeling, packaging, and advertising when the drug is marketed, to monitoring actual experience with the drug after its sale to consumers.

The high cost of research and development in this regulatory environment is a significant deterrent to new drug development. The Boston Consulting Group has estimated that the pre-tax cost of developing a medicine introduced in 1990 was $500 million.[11] A 1994 study conducted by economists at Duke University found that only three of every ten drug products, or new chemical entities, introduced from 1980 to 1984 had returns higher than average after-tax research and development costs.[12] Liability concerns also can and do drive valuable therapies from the market. These deterrents to research and

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9 Act of October 10, 1962, Pub. L. No. 87-781, 76 Stat. 780, § 102(c), codified at 21 U.S.C. § 355(d)(5).

10 See, e.g., the Durham-Humphrey Act, Pub. L. No. 82-215, 65 Stat. 648 (1951) (concerning prescription requirement); the Drug Listing Act of 1972, Pub. L. No. 92-387, 86 Stat. 559 (1972); the Orphan Drug Act, Pub. L. No. 97-414, 96 Stat. 2049 (1983); the Drug Price Competition and Patent Term Restoration Act of 1984, Pub. L. No. 98-417, 98 Stat. 1585 (1984); the Drug Export Amendments of 1986, Pub. L. No. 99-660, 100 Stat. 3743 (1986); the Prescription Drug Marketing Act of 1987, Pub. L. No. 100-293, 102 Stat. 95 (1988); the Generic Drug Enforcement Act of 1992, Pub. L. No. 102-282, 106 Stat. 149 (1992); Prescription Drug User Fee Act, Pub. L. No. 102-571, 106 Stat. 4491 (1992); Food and Drug Administration Modernization Act of 1997, Pub. L. No. 105-115, 111 Stat. 2296 (1997).

11 Industry Profile, supra note 7, at 17.

12 Id., at 18.

development are the backdrop against which the Michigan legislature enacted section 2946(5).

A. A Comprehensive Federal Regulatory Scheme Requires Pharmaceutical Manufacturers to Prove the Safety and Effectiveness of their Drug Products Before Marketing Those Products.

In the United States, a pharmaceutical manufacturer invests on average fifteen years from the time it first synthesizes a drug to the time it secures FDA permission to market the drug.[13] Over eight of those years are spent studying and testing the drug, with FDA oversight, to determine its safety and effectiveness.[14] During that period, a pharmaceutical company will undertake approximately 70 clinical trials involving more than 4000 patients.[15] We describe below the testing that a pharmaceutical manufacturer must perform to demonstrate that its drug is safe and effective and to obtain FDA approval to market that drug.

1. Pre-Clinical Testing

Before it can even begin clinical trials (testing in humans), the manufacturer (also known as the "sponsor") of a new drug must perform laboratory and animal tests adequate to demonstrate that it is safe to begin a clinical trial program. If the clinical trials

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13 Id., at 24.

14 Managing the Risks from Medical Product Use: Creating a Risk Management Framework, Report to the FDA Commissioner from the Task Force on Risk Management (May 1999) (Task Force Report) at 37; see also Steven Garber, The Institute for Civil Justice, Product Liability and the Economics of Pharmaceuticals and Medical Devices (1993) (ICJ Report) at 26 (citing 9.5 years).

15 Industry Profile, supra note 7, at 26. This is more than twice the number of trials and patients than for the new drug applications ("NDAs") submitted in the early 1980s. Id.

are successful, the sponsor may submit a new drug application ("NDA") to FDA requesting approval for marketing.

In the pre-clinical testing stage, the manufacturer conducts laboratory and animal tests to evaluate the safety of newly-synthesized compounds. If a compound appears to have important biological activity and might be useful as a drug, the manufacturer conducts special tests to assess its safety in the major organ systems. During this stage, the manufacturer conducts studies in animals to ensure that the drug is safe enough to be tested in humans. FDA regulates the laboratory work and facilities through good laboratory practice (GLP) regulations. 21 C.F.R. Part 58.

In the second stage, before performing any clinical trials, the manufacturer submits an investigational new drug application (IND) to FDA. 21 C.F.R. § 312.40. Every IND must contain sufficient pharmacological and toxicological data to show that it would be reasonably safe to conduct clinical trials in humans. 21 C.F.R. § 312.23(a)(8). An IND also must detail the drug's chemical composition, structural formula, proposed dosage form, and proposed route of administration; the investigative plan and proposed clinical trial protocols; any prior human experience (including foreign data); and prior withdrawals from investigation or marketing. 21 C.F.R. § 312.23. If FDA is satisfied that the pre-clinical animal data do not demonstrate an unacceptable safety risk to humans, the drug sponsor may begin clinical studies in humans. 21 C.F.R. §§ 312.21, 312.40.

2. Clinical Trials

During a three-phase clinical program, the drug is tested for safety and effectiveness in small doses and multiple doses, in healthy volunteers and patients, and in

varying demographic groups, in combination with a wide variety of other drugs, and in patients with varying types of organ impairment.[16]

In Phase I, the drug is given to a small number of test subjects, typically healthy volunteers, in order to determine the metabolism and pharmacologic actions of the drug in humans and the side effects associated with increasing doses and, if possible, to gain early evidence on effectiveness. 21 C.F.R. § 312.21(a)(1). Phase II investigations involve an expanded patient group—up to several hundred patients—with the disease or condition being studied. Phase II trials are designed to assess the drug's effectiveness against the targeted disease. They also explore risks and side effects, and are designed to confirm and refine early data on optimal dosage. 21 C.F.R. § 312.21(b). Phase III clinical trials commence once the drug's sponsor has gathered preliminary evidence suggesting effectiveness of the drug. 21 C.F.R. § 312.21(c). These studies can involve several thousand patients and frequently take place in multiple locations throughout the country. The goal of Phase III trials is to collect sufficient safety and efficacy data to support the new drug application for FDA approval.

FDA oversees clinical trials to protect the health and safety of the human test subjects and to ensure the integrity and usefulness of the test data. A clinical trial conducted under any IND is subject to part 312 of FDA's regulations, which include "good clinical practices" (GCP) requirements. These regulations describe the responsibilities of a sponsor during the conduct of a clinical trial. A sponsor is responsible for the selection of investigators, the submission of safety reports, the submission of annual reports, and the

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16 Industry Profile, supra note 7, at 26.

submission of protocol amendments (for example, if a new investigator is added). The sponsor is also responsible for ensuring that the trial is conducted in accordance with the protocols in the IND. To help ensure that GCP standards are followed, FDA may inspect a clinical trial site and may inspect records and reports relating to that trial. See, e.g., 21 C.F.R. § 312.58. Significant violations of the good clinical practices regulations may give FDA grounds to impose a clinical hold on the trial under 21 C.F.R. § 312.42. If the violations cast doubt on the integrity of the study results, FDA may decline to consider the study results when the NDA is filed. This program of inspections and audits, known as the Bioresearch Monitoring (BIMO) program, covers all of the parties involved in regulated clinical trials, including clinical investigators, institutional review boards (IRBs), sponsors, monitors and contract research organization. FDA conducts more than 1000 inspections annually under this program.[17]

FDA's informed consent regulations in 21 C.F.R. Part 50 apply to clinical trials. These regulations are intended to ensure that study subjects make fully informed decisions about whether to take an investigational product. Section 50.25 lists the mandatory elements of an informed consent form. 21 C.F.R. § 50.25(a). FDA's Institutional Review Board (IRB) regulations in 21 C.F.R. Part 56 also apply. The IRB regulations are intended to ensure that research subjects are informed and willing participants and that their health and safety are not unnecessarily endangered. An Institutional Review Board composed in accordance with 21 C.F.R. § 56.107 must review

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[17] "Good Clinical Practice in FDA-Regulated Clinical Trials," <www.fda.gov/oc/gcp default.htm> (visited March 9, 2002).

the proposed protocol and informed consent forms and approve the plan. FDA holds the board responsible for the ethical acceptability of the proposed research.[18] FDA inspects IRB records and operations to determine whether approvals, human subject safeguards (including informed consent), IRB membership, and the IRB's conduct of its business comply with FDA regulations.[19]

During a clinical trial, the sponsor must make continuing submissions to FDA to keep the agency apprised of developing safety and effectiveness information and any changes in the investigational plan. Thus, for example, a sponsor must submit a protocol amendment for any change in a phase 2 or phase 3 protocol that significantly affects the safety of the subjects, the scope of the investigation or the scientific quality of the study. Examples would include increases in the drug dosage, significant changes in the design of the trial (such as dropping a control group) and addition of a new investigator. 21 C.F.R. § 312.30. Any change in the protocol must also be approved by the IRB prior to its implementation. Id. The sponsor must also file IND safety reports under 21 C.F.R. § 312.32 and annual reports under 21 C.F.R. § 312.33.

3. The New Drug Application

Following the clinical trials, the drug sponsor prepares and submits an NDA, seeking FDA's permission to manufacture, distribute and market the drug in the United States. Among other things, the NDA must include:

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18 Id.

19 FDA regulations prohibit any IRB member from participating in review of a study in which the member has an interest (except to provide information). 21 C.F.R. § 56.107(e).

- preclinical data, such as laboratory and animal studies, evaluating the drug's pharmacology and toxicology, 21 U.S.C. § 355(b)(1)(A), 21 C.F.R. § 314.50(d)(2);

- data on the manner in which the drug is absorbed, distributed, metabolized and excreted in humans (i.e., pharmacokinetic and bioavailability data), 21 C.F.R. § 314.50(d)(3);

- clinical data obtained from administering the drug to humans, including data demonstrating the drug is safe under the proposed conditions of use, 21 U.S.C. § 355(d)(5), 21 C.F.R. § 314.50(d)(5);

- a description of the proposed methods by which the drug will be manufactured, processed, and packed, 21 U.S.C. § 355(b)(1)(D), 21 C.F.R. § 314.50(d)(1)(i)-(iii);

- a detailed chemical description of the drug and its active ingredient, 21 U.S.C. § 355(b)(1)(B)-(C), 21 C.F.R. § 314.50(d)(1)(i)-(iii);

- a list of each patent claiming the drug, drug product, or method of use, or a statement that there are no relevant patents making such claims, 21 C.F.R. § 314.50(h)-(i); and

- the drug's proposed labeling, 21 U.S.C. § 355(b)(1)(F), 21 C.F.R. § 314.50(e).

In addition to a written report from each individual study conducted, the NDA must contain an integrated summary of all available information received from any source concerning the safety and efficacy of the drug. The applicant also must include a presentation of both the risks and benefits of the drug. 21 C.F.R. § 314.50(c). NDAs can be composed of hundreds of volumes and can reach hundreds of thousands of pages.[20] The regulations governing NDA content are designed to provide FDA with enough meaningful information to evaluate the drug for which the NDA seeks approval. See 21 U.S.C. § 355(b); 21 C.F.R. § 314.50.

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[20] ICJ Report, supra note 15, at 28 n.62 (citing 100 volumes and 200,000 pages).

4. FDA Review of the NDA

In order for FDA to approve an NDA, FDA must find that the drug satisfies two fundamental requirements of the FDCA—that it is both "effective" and "safe." First, the sponsor must have "substantial evidence" that the drug will have the effect it purports to have, under the indicated conditions of use. 21 U.S.C. § 355(d), 21 C.F.R. § 314.105(c). "Substantial evidence" means evidence from adequate and well-controlled clinical studies. 21 U.S.C. § 355(d). Section 314.126 of FDA's regulations explains that a study is "adequate and well-controlled" if, for example, it uses a design that permits a valid comparison with a control in order to provide a quantitative assessment of drug effect. 21 C.F.R. § 313.126. FDA has issued extensive guidance on what types of studies are needed to establish effectiveness for particular diseases. Second, the drug may not be approved unless there are "adequate tests by all methods reasonably applicable to show whether or not such drug is safe for use under the conditions prescribed, recommended or suggested in the labeling thereof." 21 U.S.C. § 355(d)(1). In addition to imposing safety and effectiveness requirements, FDA regulations require that the methods used in, and the facilities used for, manufacturing, processing, packing and holding the drug substance and finished drug product comply with current good manufacturing practices and ensure the product's purity, quality, strength, identity and bioavailability. 21 C.F.R. § 314.125(b)(1). This aspect of NDA assessment can involve an inspection of the applicant's facilities. 21 C.F.R. § 314.125(b)(12).

FDA enlists experts in several scientific disciplines to review an NDA. An FDA new drug review team includes:

- ***chemists***, who focus on how the drug is made, and whether the manufacturing, controls, and packaging are adequate to ensure the identity, strength, quality, and purity of the product;

- ***pharmacologists***, who evaluate the effects of the drug on laboratory animals in the various short term and long term studies;

- ***physicians***, who evaluate the results of the clinical tests (including the drug's adverse as well as therapeutic effects) and whether the proposed labeling accurately reflects these effects;

- ***clinical pharmacologists***, who evaluate the rate and extent to which the drug's active ingredient is made available to the body and the way it is distributed, metabolized and eliminated;

- ***statisticians***, who evaluate the design of each controlled study and the analyses and conclusions of safety and effectiveness based on the study; and

- ***microbiologists***, who evaluate anti-infectives and drug products that are solutions or injectibles.[21]

FDA may also call on an advisory committee composed of prominent research and clinical specialists who advise FDA on the safety, effectiveness and appropriate labeling of drugs in a specific pharmacological class. 21 C.F.R. § 14.160(a). The task of the committee is to assess the NDA, evaluate whether additional studies are needed to support approval and respond to specific questions regarding the drug's safety and effectiveness. Advisory committees offer FDA staff the opportunity to consult with experts in drug therapy and are thus an important source of peer review for proposed FDA decisions.[22] Members of the public and consumer representatives also participate in the

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[21] See FDA's Review Team <www.fda.gov/fdac/special/newdrug/benteam.html> (visited March 9, 2002); see also Task Force Report, supra note 15, at 38.

[22] Department of Health, Education, and Welfare, Review Panel on New Drug Regulation, Final Report 52 (1977).

decision-making process.[23] Advisory committees often include other stakeholders, such as representatives of consumer groups. Moreover, members of the public and any other interested groups are able to observe the advisory committee proceedings and speak in the public sessions.[24] The advisory committee may vote to recommend approval or to recommend non-approval, of the entire application or of specific indications. It may also request specific additional data.[25]

The final decision, however, remains solely with FDA, which may accept or reject the committee's recommendation. The Agency must refuse to approve the

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23 FDAMA required that scientific, trade, and consumer organizations be given the opportunity to nominate individuals for appointment to the committees. See FD&C Act § 505(n), 21 U.S.C. § 355(n).

24 Task Force Report, supra note 15, at 81.

25 See, e.g., "Avapro Nephropathy sNDA Pulled," The Pink Sheet (February 11, 2002) at 40 (Cardiovascular & Renal Drugs Advisory Committee voted 6 to 5 against approval of new indication for Avapro); "Wyeth Rapamune May Need New U.S. Trial for Cyclosporine-Free Regimen," The Pink Sheet (January 28, 2002) at 11 (Antiviral Drugs Immunosuppressive Subcommittee Advisory Committee voted 5 to 4 not to recommend proposed Rapamune cyclosporine-free regimen); "Biotech Mergers in 2001," The Pink Sheet (January 14, 2002) at 29 (Oncologic Drugs Advisory Committee voted against approval of Matrix's head and neck squamous cell carcinoma treatment Intradose); "Gilead Viread Virology Data Will Distinguish HIV Drug in Physician Promotions," The Pink Sheet (November 5, 2001) (Antiviral Drugs Advisory Committee voted 13 to 1 not to recommend approval of Gilead's Adefovir); "Idec Zevalin Clears Committee," The Pink Sheet (September 17, 2001) at 15 (Oncologic Drugs Advisory Committee recommended approval of Zevalin for use in low-grade, follicular non-Hodgkin's lymphoma patients who are refractory to treatment with Rituxan, but voted 10 to 6 against approval for non-refractory patients); "Aventis Ketek Cardiac, Liver Safety Data to be Filed by Mid-2002," The Pink Sheet (August 6, 2001) at 8 (Anti-Infective Drugs Advisory Committee voted against efficacy of Ketek for all indications); "McNeil Antocin for Preterm Labor Requires Confirmatory Study," The Pink Sheet (April 27, 1998) at 4 (Reproductive Health Drugs Advisory Committee voted 9 to 1 that the data in the pivotal trial of McNeil's Antocin, for management of preterm labor, did not support approval of the indication being sought);

application if any of the grounds set forth in section 505(d) of the FDCA exists.[26] Institutional incentives lead to decisions that err on the side of safety.[27]

II. Liability Concerns Drive Valuable Drug Products from the Market

The high cost of and length of time involved in research and development of new drugs, the elaborate FDA approval process that follows and the uncertainty of commercial success are powerful disincentives to develop new drug products. Product liability litigation is an equal, if not greater, disincentive.

Expanding theories of liability and the proliferation of class actions have made the defense of lawsuits increasingly onerous for pharmaceutical defendants. Complex and voluminous litigation can divert company resources, and the threat of

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[26] See, e.g., "Aventis Ketek Cardiac, Liver Safety Data to be Filed by Mid-2002," The Pink Sheet (August 6, 2001) (FDA issued a "not approvable" letter for Aventis's Ketek for a tonsillitis/pharyngitis indication); "Zeldox QTC Prolongation is Less Severe than Serlect, Pfizer Tells Committee," The Pink Sheet (July 24, 2000) (Psychopharmacological Drugs Advisory Committee voted 4 to 2 in favor of approval of Serlect, but NDA was withdrawn because FDA was not satisfied safety issues had been resolved); "Anesta Actiq Detailing to 2500 Specialists to Begin in March," The Pink Sheet (November 9, 1998) at 6 (Anesta received a "not approvable" letter in November 1997 for Actiq, despite a unanimous advisory committee recommendation of approval; drug was approved after additional studies performed).

[27] See, e.g., Steven Garber, Product Liability and the Economics of Pharmaceuticals and Medical Devices 32 (1993) (arguing that economic incentives cause FDA to be overcautious when approving new drugs); Stephen Breyer, Regulation and its Reform 132 (1982) (describing incentives for FDA officials to overemphasize safety regulation). After reviewing more than 100 congressional investigations of FDA, one former chief counsel concluded, "No FDA official has ever been publicly criticized for refusing to allow the marketing of a drug. Many, however, have paid the price of public criticism, sometimes accompanied by an innuendo of corruptibility, for approving a product that could cause harm." Richard A. Merrill, "Can the FDA Do Anything Right?," Va. L. Sch. Rep., Summer 1978, at 19, 22, quoted in Sidney A. Shapiro, "Limiting Physician Freedom to Prescribe a Drug for Any Purpose: the Need for FDA Regulation," 73 N.W.U. L. Rev. 801, 813 n.86 (1978).

punitive damages, although not permissible in Michigan, can be a powerful disincentive to introduce new products to market.

Pharmaceutical companies have been particularly hard hit, due to the unique nature of their products.[28] The value of a new pharmaceutical product lies in its ability to affect the human body. The "essential value of therapeutic drugs—their capacity to treat or control diseases by affecting the human system—is also the source of their dangers."[29] Drugs not only prevent and treat disease; they can and do impair organs and functions that are essential to life and health.[30] There is, as former FDA Commissioner George Larrick once testified, "no known compound which, under certain conditions, cannot injure, destroy tissue, or cause death."[31] Moreover, clinical trials cannot identify all possible adverse reactions prior to marketing. Human beings are too biologically diverse, and infrequent adverse effects will not materialize in trials of a few hundred or few thousand patients.[32] Not surprisingly, the pharmaceutical industry is the repeated target of personal injury actions that the tort system is ill equipped to handle, particularly as pharmaceuticals

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28 See W. Kip Viscusi, et al., "A Statistical Profile of Pharmaceutical Industry Liability, 1976-1989," 24 Seton Hall L. Rev. 1418, 1434 (1994).

29 Richard A. Merrill, "Compensation for Prescription Drug Injuries," 59 Va. L. Rev. 1, 9 (1972).

30 Id.

31 Hearings on Drug Safety Before the Subcomm on Intergovernmental Relations of the House Comm. on Government Operations, 88th Cong, 2d Sess., pt. 1, at 147 (1964).

32 Clinical trials for most pharmaceutical products enroll 10,000 patients at most. In the first year of marketing, a successful new medical product can reach millions of Americans. Task Force Report, at 43; see also PhRMA, White Paper on Drug Safety in the Post-Marketing Period (November 25, 1998) <www.phrma.org/srpub/papers/11.25.98.drug.saf.html> (visited October 28, 1999).

become more complex. Juries nearly always lack the specialized experience necessary to resolve the relevant scientific issues.[33]

According to the American Medical Association, the increased liability costs for pharmaceutical manufacturers have had a "profound negative impact on the development of new medical technologies."[34] In a 1993 study on the impact of product liability lawsuits on the drug industry, the Institute for Civil Justice (ICJ) noted that innovation has the "potential to enhance future product safety and effectiveness and to reduce health care costs." Accordingly, the ICJ noted, "[e]ffects on innovative effort may be the most important element of the effects of liability on the economic performance of [the pharmaceutical and medical device] industries."[35] ICJ emphasized that liability concerns may steer industry away from types of innovation that pose large liability threats.[36]

This is precisely what has happened. The expansion of tort liability over the last twenty-five years has reduced the availability of medicines. For instance, by early 1984, all but three of the eight manufacturers of DTP vaccine had discontinued its production.[37] By the end of that year, only one manufacturer was still producing the

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33 Indeed, a prospective juror with relevant experience would almost certainly be challenged by either or both parties.

34 American Medical Association, Report of the Board of Trustees: Impact of Product Liability on the Development of New Medical Technologies 88 (1988).

35 ICJ Report, supra note 15, at 143.

36 Id. at 144.

37 Philip M. Boffey, "Vaccine liability threatens supplies," NY Times (June 26, 1984) at C1, col. 1.

vaccine—the others had discontinued production due to liability concerns. [38] Severe shortages ensued. [39] Ultimately, Congress intervened by enacting the National Childhood Vaccine Injury Act,[40] which was intended, among other things, to safeguard the supply of vaccines by protecting manufacturers from punitive damage awards.[41]

Similarly, no medicine is available in the United States for severe pregnancy-related nausea. A medicine once available—Bendectin—was removed from the market by the manufacturer following numerous lawsuits and punitive damage verdicts, despite the complete absence of solid scientific evidence of a causal connection between the medicine and birth defects,[42] and despite the fact that the manufacturer had won the vast majority of cases against it either at trial or on appeal.[43] The void in the market remains; withdrawal of Bendectin has forced doctors "to prescribe less extensively studied

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38 Stephen Engelberg, "Make of vaccine quits the market: Immunity shots for whooping cough will now be sold by only one company," NY Times (December 12, 1984) at A21, col. 1.

39 U.S.P.H.S. Interagency Group to Monitor Vaccine Development, Production, and Usage, "Diphtheria-Tetanus-Pertussis Vaccine Shortage," 253 JAMA 1540, 1541 (March 15, 1985).

40 42 U.S.C. § 300aa-1 et seq. (1986).

41 See also Walter K. Olson, The Litigation Explosion 166 (1991) ("After American trial lawyers stoked a worldwide panic over the whooping cough (pertussis) component of the diphtheria/pertussis/tetanus (DPT) vaccine, vaccination rates against whooping cough declined in Japan and parts of Europe and many children died from the disease itself.").

42 FDA acknowledged that "available data does not demonstrate an association between birth defects and Bendectin." Daubert v. Merrell Dow Pharmaceutical Co., 43 F.3d 1311, 1314 (9th Cir. 1995).

43 See Daubert v. Merrell Dow Pharmaceutical Co., 43 F.3d 1311 (9th Cir. 1995).

drugs, or perhaps nothing at all."[44] A condition once safely treatable with a pill now requires hospitalization.[45]

Product liability concerns have also driven contraceptive devices from the market and have limited the development of new contraceptives. This phenomenon has been noted by the National Research Council and the Institute of Medicine, which concluded that such concerns "have contributed significantly to the climate of disincentives for the development of contraceptive products."[46]

Imposing compensatory and, in some states, punitive damages in connection with an FDA-approved drug overrides and undoes 15 years worth of scientific testing and analysis conducted by experts in numerous disciplines. The core purpose of the NDA review process is to determine whether the benefits of a product outweigh its risks, by taking account of information such as the seriousness of the disease, the presence and adequacy of existing remedies, potential adverse reactions, and other safety data.[47] Thus, FDA approval is based on a careful determination that the risks of a particular drug are reasonable in light of the health benefits its provides.[48]

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44 Brock v. Merrell Dow Pharmaceuticals, Inc., 874 F.2d 307, 310 n.9 (5th Cir. 1989), cert. denied, 494 U.S. 1046 (1990).

45 See generally C.I. Barash & L. Lasagna, "The Bendectin Saga: 'Voluntary' Discontinuation," J. of Clinical Research and Drug Development 1, 277-292 (1987).

46 Luigi Mastroianni, Developing New Contraceptives: Obstacles and Opportunities 141 (1990); see also Institute of Medicine, Contraceptive Research and Development: Looking to the Future (Polly F. Harrison & Allan Rosenfeld, eds. 1996), at 21-23.

47 Statement Regarding the Demonstrations of Effectiveness of Human Drug Products and Devices, 60 Fed. Reg. 39180, 39180 (August 1, 1995).

48 See Merrill, supra note 31, at 10 ("Although no provision of the Federal Food, Drug, and Cosmetic Act provides that FDA may approve a drug only if the benefits outweigh the risks, this inevitably is the crux of any decision to permit a new drug to be (continued . . .)

The Court of Appeals held Section 2946(5) unconstitutional. If permitted to stand, this ruling will subject pharmaceutical products to a duplicative system of comprehensive regulation followed by litigation. Such a system can—and the American Law Institute has suggested does—impose a disproportionate burden on new processes and new products, essentially causing overdeterrence in the development of intensively regulated products.[49] Moreover, it skews a balance carefully struck by the legislators. Judicial nullification of a legislative conclusion that risks should be evaluated through a regulatory rather than judicial process imposes costs and burdens on the development of important new drugs, to the ultimate detriment of public health.[50]

III. Conclusion

The FDA approval process is governed by a comprehensive regulatory scheme that has been developed and strengthened over more than half a century. It uses the highest standards for safety and effectiveness in the world.[51] FDA reviewers include professionals with expertise in chemistry, pharmacology, pharmacokinetics, statistics and microbiology. The agency frequently works with the assistance and advice of the nation's expert scientists, and often with significant input from other stakeholders. FDA employs

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marketed or to allow an old one to remain on the market."); see also Task Force Report, supra note 15, at 34. ("A safe product is one that has reasonable risks, given the magnitude of the benefit expected and the alternatives available. . . . FDA's current efforts . . . are largely devoted to pre- and postmarketing risk assessment.").

49 II ALI Study, supra note 5, at 89.

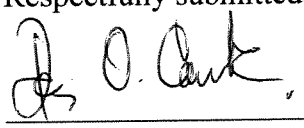
50 Id., at 86 n.8

51 "Revitalizing New Product Development from Clinical Trials Through FDA Review," Hearings on S 1477 Before the Senate Committee on Labor and Human Resources, 104th Cong., 2d Sess. 52 (1996) (testimony of Dr. Carl C. Peck).

over 1500 full-time equivalent personnel, simply to review new drug applications.[52] In light of the inadequacies of the tort system for handling complex pharmaceutical products liability actions, and in light of the fact that FDA is so well equipped to assess the comparative risks and benefits of new pharmaceutical products, pharmaceuticals present a strong case for tort deference to regulatory standards and expertise. This is the Michigan solution.

The Michigan legislature has decided that cost/benefit assessment by FDA is better than case-by-case product liability litigation and *ad hoc* and inconsistent jury assessments of drug safety. *Amicus* respectfully suggests that this is not only within the power of the legislature, but eminently practicable. The Court should therefore grant Defendants' application for leave to appeal and reverse the decision of the Court of Appeals.

Respectfully submitted,



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52 See "Agriculture, Rural Development, Food and Drug Administration, and Related Agencies Appropriations for 1999," Hearings Before a Subcommittee of the House Committee on Appropriations, 105th Cong., 2d Sess., pt. 2 at 843, 942 (1998).